# CNS Summit:

## Selected Abstracts from the 2019 Meeting

*Innov Clin Neur*. 2019;16(9–10 Suppl 1):S5–S19

## DIGITAL TOOLS AND TECHNOLOGY

### The Digital Medicine Society (DiMe): advancing the use of digital medicine to optimize health

*Authors:* Chasse R,[1] Coravos A,[1] and Goldsack JC[1]

*Affiliations:* [1]Digital Medicine Society, Boston, Massachusetts

*Objective:* We sought to advance digital medicine to optimize human health.

*Design:* Founded in 2019, the Digital Medicine Society (DiMe) is the first professional organization for experts from all disciplines covering the diverse field of digital medicine. DiMe serves professionals at the intersection of the global health care and technology communities, supporting them in developing digital medicine through interdisciplinary collaboration, research, teaching, and the promotion of best practices.

*Results:* In the four months since its launch, DiMe's membership has grown to more than 500 individuals from across the disciplines of digital medicine, located in 24 countries around the globe. Members are influencing our research agenda and participating in interdisciplinary workgroups, such as defining requirements for verification and validation processes and developing consensus recommendations on ethics in digital medicine. In addition, members have access to live webinars and workshops, collaborative and communications platforms, a crowd-sourced library of digital endpoints, events, careers services, and discounts with DiMe partner organizations.

*Conclusion:* DiMe is a professional society serving ably the digital medicine community. Together, we will drive scientific progress and broad acceptance of digital medicine to enhance public health. Join us at www.dimesociety.org.

*Funding/Disclosures:* None of the authors have any disclosures.

### Utility of an electronic, audiotaped version of the Vineland Adaptive Behavior Scale in rater quality monitoring for studies of autism spectrum disorder

*Authors:* Busner J,[1] Willgoss TG,[2] Jones E,[1] and Smith J[2]

*Affiliations:* [1]Signant Health, Wayne, Pennsylvania; [2]Roche Products Ltd., Welwyn Garden City, UK

*Objective:* We developed and validated an electronic version of the Vineland Adaptive Behavior Scale (Vineland-II) for use as a clinical outcomes assessment (eCOA) measure in international autism spectrum disorder (ASD) trials. The eCOA scale incorporates automated score conversions, administration tips such as per-item guidance from the printed manual, and built-in audio-capture and uploading capabilities to facilitate external expert review and rater remediation. The scale is currently in use as a primary efficacy measure in ongoing international child and adult ASD trials.

*Design:* As part of a clinical trial approved by an institutional review board, the parents/caregivers of children aged five to 17 years with ASD were administered the electronic Vineland-II at multiple clinic visits by qualified raters who had undergone thorough training. The interviews were audio-recorded and uploaded for quality review/remediation by an independent vendor using a priori developed quality indicators. We report here the United States pediatric results as of December 26, 2018.

*Results:* A total of 631 administrations were collected and audio-evaluated from study partners of 382 subjects at 42 clinical trial sites. Of the 631 administrations, 63 (10%) required contact/retraining with the site rater for quality concerns including administration proficiency (e.g., basal, ceiling rules), adherence to scale scoring guidance, and adherence to trained placebo response minimization guidance. When Vineland-II standard scores were evaluated in the blinded monitoring program, five sites hit predetermined criteria, triggering deeper dive reviews and additional remediation/guidance.

*Conclusion:* This is the first examination of the clinical utility of the eCOA Vineland-II in an ASD clinical trial. The results suggest that such an approach is feasible.

*Funding/Disclosures:* Busner and Jones are full-time employees of Signant Health, while Willgoss and Smith are full-time employees of Roche Products Ltd. This abstract was first presented at the American Society of Clinical Psychopharmacology Meeting in Scottsdale, Arizona, May 28–31, 2019.

### Filling in the gaps of machine learning for pharma: deep patient insights without deep learning

*Presenter:* Geraci J[1,2]

*Authors:* Leonchyk P, Tsay M, James H, and Ziauddin J

*Affiliations:* [1]NetraMark Corp, Toronto, ON, Canada; [2]Department of Molecular Medicine, Queen's University, Kingston, ON, Canada

*Objective:* We sought to evaluate whether a novel paradigm of machine learning based on a new mathematical framework was able to learn from typically sized pharmaceutical trial patient datasets. It is well-known that the most powerful machine learning methods such as ensemble tree methods and deep neural networks require massive datasets with thousands of samples. We wanted to understand if numerical-based data as found in connection with psychiatric scales, gene expression, methylation, micro-RNA, copy number variation, and microbiome data with a selection of patient cohorts (50–400 patients) could be learned from.

*Design:* Utilizing a novel machine learning technology known as DrugCrush, we tested datasets relating to Parkinson's disease, Alzheimer's disease, bipolar disorder, and aging. We allowed DrugCrush to attempt to predict subtypes from each of these datasets, with the task to explore a molecular

database and predict medications that could be repositioned, repurposed, or resurrected. We evaluated DrugCrush's performance via a measure of how suitable the chemical candidates it recommended were for each disease. The machine had access to protein interaction data that it utilized to find vulnerable locations within local protein networks via graph theory algorithms designed by our engineers.

*Results:* Despite the small datasets, the machine was capable of matching appropriate drugs for each disorder above. Further, it was able to predict drugs that were in trials for Alzheimer's disease and predicted popular available nutraceuticals for aging. Beyond such, this machine has equipped us with novel molecules that we are utilizing to design novel drug candidates.

*Conclusion:* Our experiments demonstrated there are novel algorithms capable of providing powerful machine learning to pharmaceutical companies in order to understand their patient populations better.

*Funding/Disclosures*: Not provided.

**Data in support of the Virtual Reality Functional Capacity Assessment Tool in an accepted application for the United States Food and Drug Administration Clinical Outcome Assessment Qualification Program**

*Authors:* Horan B,[1] Atkins A,[1] Pani L,[1,2] Harvey PD,[2] Clayton T,[1] Khan A,[3] Gadigian C,[1] Baldwin S,[1] and Keefe RSE[1]

*Affiliations:* [1]VeraSci, Durham, North Carolina; [2]University of Miami Miller Medical School, Miami, Florida; [3]Nathan Kline Institute, Orangeburg, New York

*Objective:* We sought to describe data supporting the successful application for the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) to enter into the United States Food and Drug Administration (FDA) Clinical Outcome Assessment (COA) Qualification Program.

*Design:* The VRFCAT is a digital performance-based outcome measure that assesses the ability to prepare a meal, shop, use transportation, and handle money, which are four of the key functional outcomes challenges in schizophrenia. It is one of only three COAs that have been accepted into the FDA COA Qualification Program, although the final qualification determination has not yet been made. Data were collected from several previous studies, including a large (n = 334) validation study of the VRFCAT in healthy controls and patients with schizophrenia that assessed cognition with the MATRICS battery (MCCB) and functional capacity with the University of California San Diego Performance-based Skills Assessment (UPSA) and a study of patients with recent-onset psychosis conducted at University of California Los Angeles.

*Results:* The VRFCAT demonstrated high sensitivity to impairment in patients versus healthy controls (d = 1.2), high test–retest reliability (intraclass correlation = 0.81), no practice effects (d = −0.04 vs. d = 0.35 for the UPSA), and large correlations with the UPSA (r = −0.56) and MCCB (r = −0.57). Similar results were found in early-phase patients, including a strong correlation with real-world functioning (r = 0.41). The VRFCAT was also found to have a low burden from the perspectives of patients and testers.

*Conclusion:* The VRFCAT demonstrates a wide range of good psychometric characteristics, convergent validity, and practical strengths that supported its acceptance into the FDA COA Qualification Program. Treatment sensitivity data are being collected from several ongoing clinical trials.

*Funding/Disclosures:* All authors are present or past employees or paid consultants to VeraSci.

**Filling the gap between available technologies and clinicians' capabilities to implement them**

*Presenters:* Rangel A[1] and Kundert K[1]

*Affiliation:* [1]VirTrial, Scottsdale, Arizona

*Objective:* We sought to understand the technology competency level of research site staff and to identify training needs to prepare them for the evolution of clinical trials and the transition to virtual visits.

*Design:* The Association of Clinical Research Professionals (ACRP) and Forte recently collaborated to conduct a "technology competency" survey of more than 1,500 site coordinators and site management team members who are responsible for both organizational strategy and day-to-day activities related to clinical trials.

*Results:* The vast majority of respondents know what is expected of them when it comes to using clinical research technology, understand why clinical research technology is necessary, and agree that their organization has structure around clinical research technology. A smaller majority (66%) agreed that they had received adequate initial training on clinical research technologies, but only 43% stated that they receive ongoing continuing education. Finally, only 35% of survey respondents said they agree or strongly agreed that their organization created new roles to help with adopting technology.

*Conclusion:* Survey results indicate that there is a gap between the available technology and the capabilities of research site staff to implement new solutions effectively, which clearly identifies a need for technology training and education.

*Funding/Disclosures:* Not provided.

**Automated sleep–wake prediction from wearable sensors using neural networks—from data collection to algorithm development, cross-validation and clinical trial deployment**

*Authors:* Wolz R,[1,2] Peraza L,[1] Joules R,[1] and Dauvilliers Y[3]

*Affiliations:* [1]IXICO, London, UK; [2]Imperial College London, London, UK; [3]Department of Neurology, Centre Hospitalier Universitaire, Montpellier, France

*Objective:* We sought to develop a convolutional neural network (CNN) to predict sleep/wake from three-axis accelerometry in order to show robustness against interdevice variability and to deploy the validated solution in central nervous system (CNS) clinical trials.

*Design:* In this study, 100-Hz three-axis accelerometry was collected alongside polysomnography for 54 elderly controls and Parkinson's disease patients. A CNN was developed and trained on the polysomnography gold standard to predict sleep/wake for every 30-second interval of preprocessed data. Cross-validation of the final algorithm was performed with an independent, publically available dataset (ICHI) through performance comparison with polysomnography and the widely established Cole–Kripke algorithm. The final algorithm was integrated into IXICO's data management

and quality control platform (TrialTracker) and deployed as an exploratory endpoint on a CNS clinical trial.

*Results:* Independent validation of the trained CNN resulted in an accuracy to predict polysomnography of 74% and 76% when validating on ICHI and the in-house dataset, respectively. This compares with outcomes of 68% and 55% achieved with the Cole–Kripke algorithm. The performance increase is largely driven by improved sensitivity in detecting individual awakenings with the CNN algorithm. The developed algorithm was successfully deployed on an ongoing phase II CNS trial, delivering good quality control performance in line with traditional algorithms.

*Conclusion:* Artificial intelligence technology can improve the analysis of accelerometry when compared with traditional, count-based measurements in a robust and reproducible way. Exploratory deployment onto clinical trials is feasible and allows one to collect the evidence needed to support further development of real-world evidence in clinical trial designs.

*Funding/Disclosures:* Wolz, Peraza, and Joules are employees of IXICO.

### Assessment of Parkinson's disease severity using machine learning

*Author:* O'Keeffe J[1]

*Affiliations:* [1]Machine Medicine Technologies Ltd., London, UK

*Objective:* Parkinson's disease (PD) is characterized in part by motor dysfunction and is commonly assessed using part III of the Movement Disorder Society (MDS) Universal PD Rating Scale (UPDRS). The proliferation of smartphones and tablets is an opportunity to pursue improved clinical management by providing an affordable and convenient way to augment human assessment.

*Design:* KELVIN-PD is a platform for the objective measurement and characterization of motor dysfunction that can be used with any camera-enabled smart device. A dataset was compiled of MDS-UPDRS motor assessments recorded using the platform as part of standard clinical examinations conducted at several partner sites in the United Kingdom and across a range of disease severities, performed by multiple assessors between November 2018 and August 2019. Random forest regressor models were trained to estimate the severity rating of the finger-tapping and hand-movement items within the MDR-UPDRS, based solely on features algorithmically extracted from 210 video assessments within this dataset.

*Results:* When tested on hidden data, both models achieved highly significant results with p-values of less than 0.001. Upon comparing the ratings made by assessors and the model, the Pearson correlation coefficient was 59% for finger-tapping and 62% for hand movements.

*Conclusion:* This result demonstrates the significant predictive power of evaluating features extracted using computer vision algorithms from a relatively small number of video assessments. Given this result, it is likely that models trained on larger datasets would meet or exceed human performance.

*Funding/Disclosures:* The author is an employee of Machine Medicine Technologies Ltd.

### The use of machine learning to drive intelligent oversight across clinical trials

*Author:* Trotta L[1]

*Affiliation:* [1]CluePoints, King of Prussia, Pennsylvania

*Objective:* This report discusses how machine learning techniques are starting to have a significant impact in supporting the unsupervised interrogation of clinical trials data to make the right decisions to ensure patient safety and data integrity.

*Design:* CluePoints provides a Central Statistical Monitoring (CSM) solution to the pharmaceutical industry. The solution utilizes statistical algorithms to assess the quality and integrity of clinical trial data. Over the last few years, CluePoints has built a large database of analyzed trials. CluePoints data analysts have analyzed and grouped detected data anomalies into signals that have been presented to and reviewed by the company's study teams. A signal is a collection of data anomalies that are potentially related to the same root cause. Among others, examples of signals include the propagation of vital signs measurements (e.g., systolic blood pressure, diastolic blood pressure, weight) across several visits, a large proportion of missing data entries in electronic case report form pages, and the over-reporting of adverse events.

*Results:* Recently, CluePoints developed a supervised machine learning algorithm to automatically suggest the grouping of data anomalies into signals. The algorithm learns from all past analyzed trials to suggest signals for a new study.

*Conclusion:* This algorithm represents an important step towards the fully automated detection of data-quality issues in clinical trials.

*Funding/Disclosures:* Not provided.

## CLINICAL RESEARCH

### Antidepressant-associated sexual dysfunction collected via prospective questionnaires: a meta-analysis of second-generation antidepressants

*Author:* Jacobsen PL[1]

*Affiliation:* [1]University of Loyola Chicago, in Chicago Illinois

*Objective:* Patient reporting of sexual dysfunction is typically low and does not accurately reflect the actual prevalence. This meta-analysis assessed the level of sexual dysfunction associated with second-generation antidepressants versus placebo as assessed via a prospective questionnaire.

*Design:* Eligible studies were randomized, double-blind, placebo-controlled antidepressant efficacy trials in patients with acute major depression that included a validated sexual functioning questionnaire. The odds ratio for developing sexual dysfunction with each antidepressant versus placebo and the standardized mean effect for sexual dysfunction for each antidepressant versus placebo were calculated. Differences by sex were assessed where data were available.

*Results:* The 17 eligible studies evaluated nine antidepressants and included either the Arizona Sexual Experiences Scale or Changes in Sexual Functioning Questionnaire. The odds of developing sexual dysfunction with paroxetine, escitalopram, and duloxetine were significantly worse than placebo in both sexes combined, while women taking desvenlafaxine and men taking vilazodone were also affected. Standardized mean effect sizes indicated significantly worse sexual functioning versus placebo for escitalopram and paroxetine with both sexes combined, which was also found in women taking escitalopram, in men taking paroxetine, and in men taking vilazodone.

*Conclusion:* Clear gender differences were seen with paroxetine, escitalopram, and vilazodone, which highlights an important consideration that antidepressants can have differential effects on sexual functioning in men and women. Conclusions are limited by the number of eligible studies.

*Funding/Disclosures*: The authors report no funding sources exist. Conflicts of interest information was not reported.

**Autonomic and central arousals in healthy controls and apneic patients—complementary aspects of the sleep-wake process?**

*Authors:* Gruber G,[1] Thiesse L,[2] Dehouck V,[2] Kirscher D,[2] Parapatics S,[1] Loretz E,[1] Friedrich S,[1] Kemethofer M,[1] Viola A,[2] and Dorffner G[1]

*Affiliations:* [1]The Siesta Group, Vienna, Austria; [2]PPRS, Colmar, France; [3]Medical University of Vienna, Section for Artificial Intelligence and Decision Support, Vienna, Austria

*Objective:* Arousals are short and transient changes of sleep depth toward wakefulness and can be identified on the level of the central nervous system ["central arousals" (CA)] using electroencephalography (EEG) as well as on the level of the autonomic nervous system. Autonomic arousals (AA) are identified primarily by analyzing the cardiac system. The aim of the current work was to compare CA and AA in healthy controls and apneic patients.

*Design:* Polysomnographic (PSG) as well as heart rate and body movement recordings were analyzed for 77 nights among 40 young healthy participants and 37 obstructive sleep apnea patients. PSG data were processed using a validated computer-assisted scoring solution (Somnolyzer; Phillips, Best, the Netherlands). For sleep analysis based on heart rate and body movement, the Somno Art software was used. All significances ($p < 0.001$) reported below were tested with t-tests for paired samples.

*Results:* The mean number of detected CA was significantly higher than the mean number of AA. This was observed in both controls and apneic patients. CA were significantly shorter for both controls and apneic patients. Additionally, 58.7% of AA were associated with simultaneously occurring CA, while 41.7% of CA were associated with an occurring AA. This was observed equally in controls and apneic patients. In simultaneously detected arousals, AA (87.1%) started significantly earlier than CA (12.9%). Again, the pattern was similar in controls and apneic patients.

*Conclusion:* CA were detected more frequently and were considerably shorter than AA. Approximately 50% of the arousals that appeared in conjunction with AA usually preceded the corresponding CA. These findings applied to both controls and apneic patients. Beyond being related events, CA and AA appear to reflect complementary aspects of the sleep-/wake process.

*Funding/Disclosures*: Dorffner, Kemethofer, Parapatics, Loretz, and Gruber are employees and shareholders and Friedrich is a shareholder of The Siesta Group, a service provider for measuring electrophysiological and actographic signals including sleep in clinical trials. Thiesse, Dehouck, Kirscher, and Viola are employees of PPRS, a strategic partnering organization for central nervous system trials.

## INVESTIGATIVE DRUG COMPOUNDS AND THERAPIES

**SXC-2023: a small-molecule activator of the cystine–glutamate antiporter and potential therapeutic for central nervous system disorders is safe and well-tolerated in phase I studies**

*Presenter:* Beyer CE[1]

*Authors:* Neary MP,[1] Lawton DG,[1] Pentikis HS,[1] Preigh MJ,[1] Pimentel-Cotter P,[1] and Beck TR[1]

*Affiliation:* [1]Promentis Pharmaceuticals, Milwaukee, Wisconsin

*Objective:* Abnormal glutamate signaling and/or oxidative stress are hallmark features of impulse control and related central nervous system (CNS) disorders marked by impaired cognitive/executive function. The cystine–glutamate antiporter (also known as System $x_{c-}$ or Sxc) is expressed primarily on astrocytes within key brain areas (e.g., the corticostriatal pathway), where it modulates glutamate neurotransmission and increases the formation of the body's primary antioxidant, glutathione. SXC-2023 is a small-molecule activator of System $x_{c-}$. In nonclinical settings, the neuropharmacological activity, mechanism of action, and safety of SXC-2023 were confirmed.

*Design:* Here, we present the clinical safety and pharmacokinetics profile of SXC-2023 from phase I single-ascending-dose and multiple-ascending-dose clinical studies in 96 healthy human volunteers.

*Results:* SXC-2023 was safe and well-tolerated. SXC-2023 exhibited a side-effect profile similar to that of the placebo group following either acute or chronic (once per day for two weeks) treatment and demonstrated a consistent, linear PK profile across a broad pharmacological dose range. Moreover, there were no serious adverse events or adverse events leading to discontinuation experienced during these studies.

*Conclusion:* Collectively, these results suggest SXC-2023 may represent a promising approach to treat various CNS disorders. Based on the nonclinical and clinical profile of SXC-2023 to date, two phase II trials have been initiated: a clinical pharmacology study involving provoked cognitive deficits and impulsive behaviors as well as a study in our first CNS indication, trichotillomania, an impulse control disorder defined by recurrent hair pulling accompanied by distress and other functional impairments.

*Funding/Disclosures:* All authors are either full-time employees or paid consultants of Promentis Pharmaceuticals.

**Propofol: preliminary evidence of rapid-acting antidepressant properties**

*Authors:* Daniel NG,[1] Daniel DT,[2] Daniel DG,[3] Flynn LC,[4] and Allen MH[5]

*Affiliations:* [1]Dartmouth College, Hanover, New Hampshire; [2]Brown University, Providence, Rhode Island; [3]Bioniche Global Development, LLC in McLean, Virginia and George Washington University in Washington DC; [4]LCF Consulting, LLC, Libertyville, Illinois; [5]University of Colorado School of Medicine, Aurora, Colorado

*Objective:* Propofol (2,6-diisopropylphenol) is an intravenous anesthetic agent commonly administered in ambulatory settings because of its rapid onset, dose-related hypnotic effect, rapid recovery, and favorable safety profile. Propofol has NMDA and GABA receptor affinity, in common with other recently approved and putative rapid-onset antidepressants. Anecdotal reports have described a positive

impact on mood and sociality upon awakening from propofol anesthesia.

We tested acute propofol treatment alone and in combination with subchronic fluoxetine dosing on forced swim test (FST) performance, a commonly used rodent model of depression/despair.

*Design:* Seventy-two adult male mice (C57/BL6, CRL-provided) were pretreated daily with saline or fluoxetine (20 mg/kg, intraperitoneally) (21 days for cohort 1; 24 days for cohort 2). At 24 hours after the last pretreatment injection, the mice received saline or propofol (35–50 mg/kg, intraperitoneally) treatment. Then, 45 minutes later, the mice underwent a five-minute FST. Immobility time was quantified and evaluated with a custom video-analysis software. Experiments were performed at Charles River Laboratories in San Francisco, California. Grubb's test was used to identify statistically significant outliers, which were excluded from data analysis.

*Results:* A one-way analysis of variance indicated a statistically significant effect of propofol on immobility time for cohorts 1 and 2, combined. Comparison using the Dunnett's method revealed that propofol 50 mg/kg ($p < 0.05$) but not 35 mg/kg ($p$ = not significant) reduced immobility time when compared with the saline–saline control group (difference of means of 38.42 and 16.46 seconds, respectively).

*Conclusion:* Although tentative unless replicated, the results of the current experiment are consistent with an animal model of rapidly acting antidepressant or increased resiliency effect. Given the positive results of a pilot study by Mickey et al. (2018) of EEG-guided administration of propofol for treatment-resistant depression, additional exploration of potential antidepressant effects of propofol seems warranted.

*Funding/Disclosures*: Not provided.

### Ecopipam, a selective $D_1$ antagonist in development for the treatment of Tourette's syndrome in children and adolescents: the Phase IIb D1AMOND study design

*Authors:* Mahableshwarkar AR,[1] Kim D,[1] Wanaski S,[1] Swalec J,[1] and Cunniff T[1]

*Affiliations:* [1]Emalex Biosciences, Chicago, Illinois

*Objective:* We sought to present a phase IIb study design evaluating the efficacy and safety of ecopipam in children and adolescent subjects with Tourette's syndrome (TS).

*Methods:* This is a multicenter, placebo-controlled, double-blind, randomized parallel-group phase IIb study conducted to evaluate the efficacy and safety of ecopipam tablets in children and adolescents with TS. Ecopipam is a selective D1 antagonist designed to provide D2-like efficacy while minimizing D2-related adverse events. A previous phase IIa, randomized, double-blind, placebo-controlled crossover study demonstrated preliminary efficacy of ecopipam for the treatment of children and adolescents with TS without resulting in extrapyramidal or metabolic adverse events or weight gain.

This study will enroll patients with TS aged six to 17 years of age weighing more than 18 kg with both motor and vocal tics that cause impairment in normal routines and scoring more than 20 points on the Yale Global Tic Severity Score Total Motor and Phonic Tic Score (YGTSS-TTS) who are not currently on any anti-tic medications. The study will exclude patients with significant medical or psychiatric disease. Following a screening period, subjects will be randomized to ecopipam 2 mg/kg or matching placebo and titrated to the effective dose over four weeks, followed by an eight-week treatment period.

*Results:* Seventy-five subjects per group will be enrolled in the study. The primary endpoint will be the change from baseline to Week 12 in the YGTSS-TTS. The key secondary endpoint will be the change from baseline to Week 12 in the Clinical Global Impression of Tourette's Syndrome Severity. Other secondary endpoints will include the YGTSS Impairment Score, Total YGTSS, Clinical Global Impression Improvement, and other quality of life measures. Safety assessments will include adverse events; vital signs; and measurements of akathisia, abnormal involuntary movements, suicidality, anxiety, depression, and obsessive-compulsive disorder. The poster will present baseline demographics, safety, and efficacy evaluation scales data from approximately 15 subjects.

*Conclusion:* This study is designed to determine if ecopipam, a selective D1 antagonist, can provide efficacy in the treatment of TS and to further characterize the safety profile of this drug in children and adolescent patients.

*Funding/Disclosures:* Not provided.

### Ecopipam in the treatment of stuttering

*Presenter:* Hoffmeyer D[1]

*Authors:* Maguire GA,[2] LaSalle L,[3] Nelson MA,[2] Lochhead JD,[2] Davis K,[2] Burris A,[2] and Yaruss JS[2]

*Affiliations:* [1]CI Trials, Bellflower, California; [2]University of California Riverside School of Medicine, Riverside, California; [3]University of Redlands, Redlands, California

*Objective:* This study sought to examine the efficacy and tolerability of ecopipam in adults with childhood-onset fluency disorder (stuttering).

*Design:* This was an open-label study.

*Results:* Ecopipam was well-tolerated, with no reported or observed treatment-emergent adverse events. Patients with "moderate" stuttering (#1, 7, 8) made significant gains in reading and spontaneous speaking fluency. When considering the percentage of syllables stuttered (%SS) according to the Stuttering Severity Instrument, fourth edition (SSI-4), a 40% to 50% reduction from baseline was noted among those with moderate to mild stuttering. Separately, patients with severe stuttering (#5, 10) showed surface-level fluency gains (15%–17% reduction in %SS). In particular, participant #10 showed a 76% decrease from baseline induration, while participant #5 showed gains in total scores for both the Overall Assessment of the Speaker's Experience of Stuttering for Adults and SSS, suggesting an attitudinal improvement.

*Conclusion:* This study investigated the efficacy of ecopipam among adults with childhood-onset fluency disorder (stuttering). The secondary purpose of this study was to determine the tolerability of this investigational medication not yet approved by the Food and Drug Administration using an open-label procedure to provide preliminary data. The findings support the need for a double-blind and randomized controlled clinical trial to examine the efficacy of ecopipam in the treatment of stuttering as a breakthrough therapy for a disease that currently has no medication approved.

*Funding/Disclosures:* The authors report no funding sources or conflicts of interest exist.

## MOBILE TECHNOLOGY

### A novel text message intervention to improve adherence to stimulants in attention-deficit/hyperactivity disorder

*Presenter:* Biederman J[1]

*Affiliation:* [1]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

*Objective:* The present study sought to assess the effectiveness of a novel text messaging intervention aimed at improving adherence to stimulant medications in both children and adults with attention-deficit/hyperactivity disorder (ADHD).

*Design:* Adult subjects were newly referred unmedicated adults with a Diagnostic and Statistical Manual of Mental Disorders, fifth edition diagnosis of ADHD, 18 to 55 years of age, while pediatric subjects were randomly selected children age six to 12 years who were prescribed a stimulant medication for ADHD treatment. Comparators for both groups were selected from the Partners HealthCare electronic medical records (EMR) who had been prescribed stimulant medications within the same time frame. A patient was considered adherent if a stimulant prescription was issued within 90 days of the start date of the text messages for the SMS group or within 90 days of the index prescription (defined as the first prescription for a stimulant during the study period) for the EMR group.

*Results:* Among the children, results showed that 94% of the SMS intervention group refilled their prescriptions in a timely manner as compared with only 50% of the EMR patients receiving treatment as usual. In adults, 91% of the SMS intervention group refilled their prescriptions in a timely manner as compared with only 43% of the EMR patients receiving treatment as usual. In both groups based on a number needed to treat of three, for every three patients who receive the SMS intervention, we can keep one engaged in their stimulant treatment.

*Conclusion:* These findings indicate that a novel ADHD-centric digital health intervention using SMS significantly improved the poor rate of adherence to stimulant treatment in both adults and children with ADHD, providing strong support for the utility of this readily accessible, inexpensive and widely available technology.

*Funding/Disclosures*: Not provided.

### Technical and clinical validation of smartphone-based measurement of visual and voice biomarkers of central nervous system functioning

*Presenter:* Galatzer-Levy IR[1,2]

*Affiliations:* [1]AiCure, New York, New York; [2]New York University School of Medicine, New York, New York

*Objective:* Visual markers including facial expression and gross motor movement as well as voice markers including pitch, tone, and rate of speech have both neurobiological and clinical correlates across diverse central nervous system (CNS) disorders. The objective of this study was to determine whether the remote assessment of visual and voice markers via smartphones can increase the scalability and accuracy of clinical assessment across disorders and provide a source for sensitive transdiagnostic measurement of CNS functioning that can be utilized to both develop treatments and spot clinical risk.

*Design:* For technical validation, we built a data-processing pipeline to filter noise and label video and audio footage. We passed video images that had been independently labeled for movement and facial expressivity [i.e., facial action units coding (FACs)] as well as tones captured outdoors with naturalistic light and noise. The accuracy of labeling was compared to known values. For clinical validation, we examined whether visual and voice markers differentiated patients with negative symptoms of schizophrenia ($n = 19$) from matched healthy controls ($n = 9$) and correlated with the severity of negative symptomatology using data from a brief (two-minute) automated video interview captured remotely.

*Results:* FACS labeling achieved 100% accuracy and significant separation was demonstrated between movement and nonmovement states. Further, 18 tones measured across two octaves demonstrated a mean labeling accuracy of 98.3 (C.I. = 0.01). Visual features of head movement, facial expressivity, tone, pitch, rate of speech significantly differentiated cases from controls all at $p < 0.01$. Of note, head movement, strongly tracked with negative symptoms ($\mu HC = 2.49$ mm/frame, $\mu scz = 1.52$ mm/frame; t-test $p = 0.04$), Positive and Negative Syndrome Scale—G total ($r = -0.47$; $p = 0.01$), N-total ($r = -0.44$; $p = 0.01$), excitement ($r = 0.16$; $p = 0.4$), N1 blunted affect ($r = -0.50$; $p = 0.007$), mannerisms and posture ($r = -0.41$; $p = 0.03$), and motor retardation ($r = -0.53$; $p = 0.004$).

*Conclusion:* Visual and voice markers can be accurately measured in the wild using smartphones. These markers demonstrate construct validity. In particular, visual markers are a robust, theory-driven, scalable, and underutilized source of clinical information. The technical and clinical validation of visual and voice markers collected over a smartphone provides a unique opportunity to both increase the accuracy and reduce the burden in the measurement of CNS functioning in clinical trials and real-world clinical settings.

*Funding/Disclosures*: This research was funded by AiCure. Galatzer-Levy is an employee of AiCure.

### Virtual Siteless Technology Open Research study shows the feasibility of capturing clinical trial patient data using home-based mobile devices and telemedicine

*Presenters:* Sablinski T[1] and Wong S[1]

*Affiliation:* [1]Transparency Life Sciences, New York, New York

*Objective:* We sought to ascertain the usability, viability, and patient satisfaction with collecting clinical data in the patient's home using medical mobile technologies and video telemedicine assessments as part of virtual, siteless clinical trials.

*Design:* The study enrolled 35 healthy volunteers for three virtual visits with research staff using the Transparency Virtual Trials™ software platform (Transparency Life Sciences, New York, NY, USA). The primary outcome measure was an assessment of participants' experiences during the study. The study also assessed the completeness of captured data and the suitability of the approach for implementation in clinical trials. Participants used mobile devices and telemedicine technologies for teleconsent and to transmit vital signs (e.g., blood pressure, heart rate, body weight), safety (cardiac), and efficacy (pulmonary function) data that are commonly captured in clinical trials. There was no experimental treatment.

*Results:* The Virtual Siteless Technology Open Research (VISITOR) study demonstrated that subjects were able to use telemedicine devices

during a virtual study visit to accurately capture clinical trial data. Compliance in completing the study visits was high and participants reported high levels of satisfaction with the trial experience.

*Conclusion:* VISITOR is the first clinical study to integrate teleconsent, patient scheduling, and telemedicine-supervised at-home data collection. The results confirm that virtual trials are feasible, accurate and well-received by participants.

*Funding/Disclosures:* Sablinski and Wong are employees of and are equity shareholders in Transparency Life Sciences.

## PATIENT ASSESSMENT

### Electroencephalography biomarkers for tracking disease progression and evaluating response to investigative therapeutics in Alzheimer's disease and mild cognitive impairment

*Authors:* Waninger S,[1] Meghdadi A,[1] Karic M,[1] Angelopolous E,[1] and Berka C[1]

*Affiliation:* [1]Advanced Brain Monitoring, Carlsbad, California

*Background:* Neurophysiological metrics including quantitative electroencephalogram (EEG) and event-related potentials (ERPs) reliably measure the physiology associated with resting state and cognition and may provide sensitive metrics for early diagnosis, tracking disease progression and assessing the efficacy of novel interventions for dementia.

*Objective*: This study aimed to evaluate the effectiveness of EEG and ERPs in assessing early Alzheimer's disease (AD) and MCI.

*Design:* Resting-state EEG data with five minutes of eyes open and five minutes of eyes closed were acquired from a cohort of Alzheimer's disease subjects as compared with healthy controls (HC) and benchmarked against $^{18}$F-fluorodeoxyglucose positron-emission tomography. A standard image recognition task (SIR) was administered with concurrent EEG acquisition to elicit ERPs in MCI and healthy cohorts. EEGs were filtered and independent component analysis applied.

*Results:* The hallmark "slowing" of EEG was observed as an enhancement of slow bandwidths, particularly theta, and a suppression of higher bands, including alpha, in the AD cohort versus HC. Significant correlations were identified between EEG metrics and regions of glucose hypometabolism in AD patients including the cingulate gyrus and precuneus. There were significant decreases observed in the ERP waveform late-positive component in the MCI group versus the HC during a memory task with significant decreases over the central, temporal, parietal, and occipital regions.

*Conclusion:* The data suggest that resting-state EEG and cognitive ERPs obtained during tasks that activate the neural circuits involved in sustained attention and recognition memory may provide a powerful tool for assessing early AD and MCI and have a strong potential as sensitive and robust biomarkers for tracking disease progression and evaluating response to investigative therapeutics.

*Funding/Disclosures*: All authors are employees of Advanced Brain Monitoring Inc. Berka is also a shareholder of Advanced Brain Monitoring Inc.

### Consequences of administering the Clinical Global Impression Scale out of order

*Authors:* Daniel DG[1] and Kott A[1]

*Affiliation:* [1]Signant Health, Wayne, Pennsylvania

*Objective:* The Clinical Global Impression Scale (CGI) is the investigator's overall assessment of the severity of symptoms and functional impairment caused by a disease. It is recommended to be administered after other efficacy scales so that the investigator's assessment will be informed of all available information about the subject's condition. In the current retrospective analysis, we assessed whether an incorrect administration order of the CGI was associated with discrepancies between the CGI and the primary outcome measure.

*Design:* Our dataset was pooled from 11 clinical outcomes assessment trials. For the purposes of the analysis, we limited the dataset to eight trials where the CGI was administered in am incorrect order in at least 1% of visits and where meaningful relationships between CGI and the primary outcome was expected. Within each trial, we identified as discordant those raw and change data where the actual primary efficacy score differed by at least two standard deviations from the expected score after linear regression with the CGI-S score was used as a predictor variable. Logistic regression was then used on pooled data to explore whether the incorrect order of CGI administration increased the odds of a discordant rating.

*Results:* The data were drawn from 59,270 visits with CGI and primary efficacy outcome data available in 54,212 visits. The CGI was administered out of order in 4.1% of data. Discrepancies between CGI-S and the primary efficacy outcome were identified in 5% of data and discrepancies between change from baseline in CGI-S and in the primary efficacy outcome was observed in 4.8% of the data. The presence of incorrectly administered CGI increased the odds of raw score discrepancy 1.4-fold (95% confidence interval: 1.2–1.7) and the odds of discrepancy in change from baseline 1.3-fold (95% confidence interval: 1.1–1.6), both significant with $p < 0.01$.

*Conclusion:* We have previously described quality indicators associated with data errors, increased placebo response, and decreased drug–placebo separation. In the current analysis, we found that the incorrect order of administration of the CGI was associated with significantly increased odds of discordances, both in the raw and in the change data. Errors in the order of administration of the CGI versus other scales can be prevented by utilizing clinical outcomes assessment to mandate the order of scale administration.

*Funding/Disclosures*: Not provided.

### Recall periods used in patient-reported outcomes need specificity: patients have a varied understanding of the meaning of 'today'

*Presenters:* Dias N[1] and Dallabrida SM[1]

*Affiliation:* [1]ERT, Boston, MA, USA

*Objective:* We sought to identify patients' understanding of the word "today," a recall period often used in patient report outcomes (PROs).

*Design:* Participants (n = 589) from the general population completed an online survey. Respondents were asked, "if you were asked to report about the symptoms you experienced today, what time frame would you think about when providing your answer?," and then provided five options to choose from.

*Results:* The majority of the respondents (74% female) indicated that they would "think about the moment they woke up to the moment they answered the question"

(46%); however, this was closely followed by "the past 24 hours" (37%). These answers alone represent two very different periods of time that a patient may consider when reporting symptoms. The remaining answers as follows confirmed further a variability in interpretation: "from 12:01 am to the moment you answered the question" (8%), "the meaning of TODAY is unclear to me and I would need more detailed information" (6%), and "the past few hours" (3%).

*Conclusion:* PROs are important measures of treatment benefit in clinical trials, but each question must be properly understood by the patient in order to provide evidence of meaningful change in health status. The recall period of 'today' is often provided; however, these data show patients do not understand the exact period of time to consider. Therefore, data provided by patients in these PROs may prove inaccurate. These results suggest that patients would benefit from additional instruction/training of the recall period being requested in each PRO assessment.

*Funding/Disclosures*: The authors are both employees of ERT.

### Patient misunderstanding of how to report pain and swelling

*Authors:* Dumais KM[1] and Dallabrida SM[1]

*Affiliation:* [1]ERT, Boston, Massachusetts

*Objective:* Drug approvals for osteoarthritis (OA) are predominantly based on patient-reported outcomes (PROs), making accurate self-reporting of symptoms critical to determine drug efficacy. Yet, how to report the major PRO items in OA studies (e.g., pain, swelling) may not be well-understood by patients.

*Design:* Participants from the general public were surveyed online and asked to imagine being in a clinical trial for OA of the knee. Participants were asked what they would consider when reporting the severity of their knee pain (n = 534) or the swelling in their knee (n = 530) at its worst during the past 24 hours. Response options included "pain"; "swelling"; and various other combinations such as "pain and swelling," "swelling and stiffness," or "all of the above."

*Results:* Only 28% of participants correctly chose that they would only consider their symptom of pain when asked to report their knee pain. Instead, most reported that they would consider multiple symptoms (e.g., pain, swelling, stiffness) (66%) when reporting their knee pain. Similarly, only 42% correctly chose that they would only consider their symptom of swelling when reporting on knee swelling, while most reported that they would consider multiple symptoms (e.g., swelling, stiffness, pain) when reporting their knee swelling (58%).

*Conclusion:* Our results suggest that most participants are inaccurately thinking about more than just pain or swelling when answering questions about these symptoms. Training patients on how to report their pain, swelling, or other OA symptoms may help to increase patient understanding and improve data accuracy.

*Funding/Disclosures:* Both authors are employees of ERT, who funded this research.

### Is the Clinical Global Impression Scale truly administered last?: an exploratory analysis of scale administration order

*Authors:* Kott A[1] and Daniel DG[1]

*Affiliation:* [1]Signant Health, Wayne, Pennsylvania

*Objective:* Among the benefits of clinical outcomes assessment (eCOA) systems, the availability of interview start times offers a unique insight into the way scales are administered at any visit. The Clinical Global Impression Scale (CGI) synthesizes all information available from the subject, caregivers, and medical notes and is therefore typically required to be rated last. The purpose of this analysis was to explore how often the CGI was actually administered last across a number of eCOA studies.

*Design:* Our dataset was pooled from 11 eCOA clinical trials. Within each visit, we determined whether or not the CGI scale was administered last. Descriptive statistics were obtained for the overall sample, for each study and indication. Additionally, we explored the possible association between the percentage of visits with inappropriately administered CGI and the complexity of the study as reflected in the number of eCOA scales utilized.

*Results:* Among the 62,663 visits collected, the CGI was administered 58,484 times. In the overall sample, the CGI was not administered in the correct order in 4% of visits. Significant differences were noted among indications ($p < 0.001$) and individual protocols ($p < 0.001$). Additionally, a statistically significant relationship was observed between study complexity and inappropriate order of CGI administration ($p < 0.001$).

*Discussion:* Our data indicate that CGI is often administered in the wrong order during a visit. This is especially true in studies using five or more rating instruments. Intelligent eCOA systems allowing for preprogrammed the sequence of scale administration and completing built-in checks offer a simple solution for how to prevent these types of errors.

*Funding/Disclosures*: Both authors are full-time employees of Signant Health.

## SUICIDALITY

### Project Starr 911: a model for researchers to engage in suicide prevention

*Authors:* Hendry P,[1] Armstrong K,[2] Barag J,[2] Fowler C,[3] Gutierrez N,[4] Harkavy-Friedman J,[5] Perez E,[3] Vanover K,[6] and Kramer L[7]

*Affiliations:* [1]Mental Health America, Alexandria, Virginia; [2]Premier Research, Trenton, New Jersey; [3]Otsuka Pharmaceuticals, Tokyo, Japan; [4]Pillar Research, Richardson, Texas; [5]American Foundation for Suicide Prevention, New York, New York; [6]Intra-Cellular Therapies, Inc., New York, New York; [7]The STARR Coalition, Little Rock, Arkansas

*Objective:* A strong link exists between mental illness and suicide. Up to 20% of individuals with a diagnosis of mental illness die by suicide. Approximately 90% of those who complete suicide experience mental illness. People considering suicide usually seek help: approximately 64% of individuals who attempt suicide visit a doctor within a month before their attempt. Having a chronic condition increases the odds of suicide by 363%. Clinical research call centers field thousands of calls on a yearly basis. The purpose of project STARR 911 is to build collaboration between clinical research and suicide prevention efforts.

*Design:* To achieve the above, the first step is to identify current practices. Thus, we surveyed clinical research sites to identify current practices for recognizing and taking action for callers who report suicidal ideation.

*Results:* Preliminary results indicated that some clinical research sites have scripts for their call centers and suicide hotline

information readily available. It was generally agreed that national experts in suicide prevention are preferred referral sources over local resources that can be variable in terms of accessibility and quality. Script suggestions included asking about intent to act and to determine how long the caller has felt suicidal, to determine the acuity. Creating a designated "warm" line for call centers.

In response to the limited process identified, Project 911 will further determine intervention resources that could be provided to callers. A short script and best practices for recognition and de-escalation as well as a brief training program that could be made widely available and implemented will be developed. For example, a suicide prevention program can be disseminated at investigator meetings. A tracking system to record the number of successful referrals or "warm" hand-offs to suicide prevention specialists will be implemented, if possible.

*Conclusion:* Research can be a part of the solution to suicide prevention. Potential suicidal ideation or behavior can be identified through clinical research call centers and referred to national suicide prevention experts in a systematic way for broad-reaching impact.

*Funding/Disclosures:* The authors report conflicts of interest exist. Funding information was not reported.

### Is dimensional scale data more sensitive than categorical data in detecting an antisuicidality efficacy signal?—a case study

*Authors:* Giddens JM[1,2] and Sheehan DV[1–3]

*Affiliations:* [1]Harm Research Institute, Tampa, Florida; [2]Tampa Center for Research on Suicidality, Tampa, Florida; [3]University of South Florida College of Medicine, Tampa, Florida

*Objective:* This case study reports the relative merits of using a categorical system and dimensional scale data to track the efficacy of an antisuicidality treatment.

*Design:* A 31-year-old female subject who had experienced suicidality almost daily for more than 20 years prospectively collected a self-report data series over 80 weeks using the Sheehan Suicidality Tracking Scale (S-STS), covering a timeframe before and during effective treatment for suicidality.

*Results:* The S-STS (dimensional) showed an efficacy signal as early as two to six weeks. The categorical data took between 14 and 21 weeks to show an efficacy signal. The "most time spent in suicidality per day" measure was more sensitive in detecting the efficacy signal (or a loss of efficacy) than, in rank order (1) the "usual time spent in suicidality per day," (2) the "least time spent in suicidality per day," (3) both the active and passive suicidal ideation event counts, and 94) the highest United States Food and Drug Administration–Central Atlantic States Association of Food and Drug Officials 2012 category endorsed for the week.

*Conclusion:* For every category studied, there was a further delay of between 10 and 17 weeks in the ability of the categorical data to detect the antisuicidality efficacy signal compared to the corresponding dimensional scale data. This has implications for the design of antisuicidality treatment efficacy (and safety) outcome measures. The inclusion of a dimensional suicidality scale also increases the likelihood of serendipitously finding antisuicidality efficacy while investigating candidate drug treatments for other central nervous system indications.

*Funding/Disclosures:* Sheehan is the author, copyright and patent holder of scales (including S-STS), structured interviews, phenomena definitions, classifications, and books on suicidality; a nonlinear model and candidate drug treatments for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. He is a co-founder of Harm Research Institute and Harm Research Press and owns stock in and is a consultant for Nview Health, which distributes the computerized versions of his scales and structured interviews. Sheehan receives royalties from the licensing of his Suicidality measures. He is a consultant for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Seelos, Biogen, and Eisai and a presenter for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Biogen, and Eisai. Giddens is the author and copyright holder of scales, phenomena definitions, classifications, and books on suicidality; a nonlinear model and a candidate drug treatment for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. She is a cofounder of Harm Research Institute and Harm Research Press and is the editor of the *Science of Suicidality*. She is a consultant for Nview Health and Biogen.

### The graphic display of quantitative suicidality data: suicidality plots

*Authors:* Giddens JM[1,2] and Sheehan DV[1–3]

*Affiliations:* [1]Harm Research Institute, Tampa, Florida; [2]Tampa Center for Research on Suicidality, Tampa, Florida; [3]University of South Florida College of Medicine, Tampa, Florida

*Objective:* Regulatory agencies, pharmaceutical companies, clinical research organizations, data safety monitoring boards, and medical safety officers are challenged with the difficulty of summarizing the suicidality status of patients under their care. Linking such data to study stopping rules is a complex multistep series of tasks, fraught with potential errors. In the interest of reducing errors, speeding up detection, ensuring the protection of patients, and maintaining the clarity of data presentation and display, there is a need for a more efficient, clear, and simple system to display suicidality data.

*Design:* We reviewed graphic displays of quantitative data in other medical and scientific disciplines to find suitable models. We applied a variety of graphic displays to a prospectively collected dataset using the Sheehan Suicidality Tracking Scale (S-STS).

*Results:* Suicidality plots (S-plots) can be used to display the data for groups of patients and for individual patients over time. Interpretation of these S-plots can quickly identify patients at higher risk and provide a method to monitor the status of patients within a large sample over time. Interpretation of S-plots can quickly identify the overall status of suicidality in the study over time in relation to the study cessation rules. The graphic display of quantitative suicidality data can be used to quickly visually identify individual patients at high risk and whether a clinical trial should be halted because of treatment-emergent suicidality.

*Conclusion:* The use of S-plots may reduce the potential medicolegal hazards from either the delayed analysis or delayed detection of suicidality in safety data, and the risk to patients in research trials and clinical settings.

*Funding/Disclosures:* Sheehan is the author, copyright and patent holder of scales (including S-STS), structured interviews, phenomena definitions, classifications, and

books on suicidality; a nonlinear model and candidate drug treatments for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. He is a co-founder of Harm Research Institute and Harm Research Press and owns stock in and is a consultant for Nview Health, which distributes the computerized versions of his scales and structured interviews. Sheehan receives royalties from the licensing of his Suicidality measures. He is a consultant for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Seelos, Biogen, and Eisai and a presenter for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Biogen, and Eisai. Giddens is the author and copyright holder of scales, phenomena definitions, classifications, and books on suicidality; a nonlinear model and a candidate drug treatment for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. She is a cofounder of Harm Research Institute and Harm Research Press and is the editor of the *Science of Suicidality*. She is a consultant for Nview Health and Biogen.

**Suicidality: a linear or a nonlinear progression over time?**

*Authors:* Giddens JM[1,2] and Sheehan DV[1–3]

*Affiliations:* [1]Harm Research Institute, Tampa, Florida; [2]Tampa Center for Research on Suicidality, Tampa, Florida; [3]University of South Florida College of Medicine, Tampa, Florida

*Objective:* We sought to investigate whether the progression of suicidality phenomena over time is linear or nonlinear. The model of progressive, linear suicidality is a long-standing assumption in suicidality research. Understanding the progression of suicidality over time will help researchers build better predictive models of suicidality.

*Design:* We adapted methods developed by Robert Stetson Shaw, a physicist at the University of California at Santa Cruz, to analyze the progression of suicidality phenomena in two continuous data sets from a single case over time. These methods are used in nonlinear dynamics theory/nonlinear systems theory/turbulence theory/deterministic chaos and permit data to be graphically displayed in two- and three-dimensional space over time.

*Results:* The method permitted the mathematical graphic modeling of suicidality phenomena over three years in the form of two- and three-dimensional attractor plots. The results showed a nonlinear dynamic progression of suicidality phenomena over time. There was no linear progression in the rate of change in the relationship between suicidal ideation and behavior observed over time.

*Conclusion:* The trajectory of suicidal phenomena over time is nonlinear and dynamic. These data are displayed graphically as attractor plots that reflect the underlying structure of suicidality and its dynamic, turbulent change over time. To improve predictive models of suicidality, progressive, linear models need to be abandoned in favor of nonlinear, mathematical modeling of dynamic systems that more accurately reflect the turbulence, unpredictability, and dynamic nature of the complex systems of suicidality phenomena as they move through time.

*Funding/Disclosures:* Sheehan is the author, copyright and patent holder of scales (including S-STS), structured interviews, phenomena definitions, classifications, and books on suicidality; a nonlinear model and candidate drug treatments for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. He is a co-founder of Harm Research Institute and Harm Research Press and owns stock in and is a consultant for Nview Health, which distributes the computerized versions of his scales and structured interviews. Sheehan receives royalties from the licensing of his Suicidality measures. He is a consultant for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Seelos, Biogen, and Eisai and a presenter for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Biogen, and Eisai. Giddens is the author and copyright holder of scales, phenomena definitions, classifications, and books on suicidality; a nonlinear model and a candidate drug treatment for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. She is a cofounder of Harm Research Institute and Harm Research Press and is the editor of the *Science of Suicidality*. She is a consultant for Nview Health and Biogen.

**Case study of magnesium in the treatment of impulse attack suicidality disorder**

*Authors:* Giddens JM[1,2] and Sheehan DV[1–3]

*Affiliations:* [1]Harm Research Institute, Tampa, Florida; [2]Tampa Center for Research on Suicidality, Tampa, Florida; [3]University of South Florida College of Medicine, Tampa, Florida

*Objective:* This case study reports on the effect of high magnesium oxide coupled with reduced dietary calcium intake (+Mg-Ca) in the treatment of impulse attack suicidality disorder (IASD).

*Design:* Using several sensitive assessment instruments such as the Sheehan Suicidality Tracking Scale (S-STS), S-STS Clinically Meaningful Change Measure (CMCM), Tampa—Classification Algorithm for Suicidality Assessment (T-CASA), and Suicide Plan Tracking Scale (SPTS) for suicidality phenomena and suicidality event monitoring, the authors tracked the effect on suicidality of magnesium oxide in doses up to 1,000 mg/day in four divided doses daily, coupled with a reduced dietary intake of calcium below 300 mg/day (< 30% of the recommended daily intake). The T-CASA was rated daily, while the S-STS, the S-STS CMCM, and the SPTS rated weekly over a 166-week (3.2-year) period covering 43,690 separate suicidality events. The subject had a 25-year history of daily suicidality that had not responded to any prior treatment including 11 antidepressants, atypical antipsychotics, anticonvulsant mood stabilizers, and lithium.

*Results:* The +Mg-Ca completely eliminated the subject's suicidality. After six months free of suicidality, the subject stopped the magnesium while maintaining the low calcium intake. Within 48 hours, she experienced a full relapse of all her prior suicidality and suicidal impulse attacks. This worsened over the ensuing week. On restarting the magnesium oxide, the suicidality decreased over the following eight days, after which point, she remained suicidality-free for the ensuing seven months.

*Conclusion:* The data from this case study suggest that high doses of magnesium oxide coupled with reduced dietary calcium intake merits further investigation for the treatment of impulse attack suicidality disorder in large double-blind, placebo-controlled studies.

*Funding/Disclosures:* Sheehan is the author, copyright and patent holder of scales (including S-STS), structured interviews, phenomena definitions, classifications, and

books on suicidality; a nonlinear model and candidate drug treatments for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. He is a co-founder of Harm Research Institute and Harm Research Press and owns stock in and is a consultant for Nview Health, which distributes the computerized versions of his scales and structured interviews. Sheehan receives royalties from the licensing of his Suicidality measures. He is a consultant for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Seelos, Biogen, and Eisai and a presenter for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Biogen, and Eisai. Giddens is the author and copyright holder of scales, phenomena definitions, classifications, and books on suicidality; a nonlinear model and a candidate drug treatment for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. She is a cofounder of Harm Research Institute and Harm Research Press and is the editor of the *Science of Suicidality*. She is a consultant for Nview Health and Biogen.

### A classification of suicidality disorder phenotypes

*Authors:* Giddens JM[1,2] and Sheehan DV[1–3]

*Affiliations:* [1]Harm Research Institute, Tampa, Florida; [2]Tampa Center for Research on Suicidality, Tampa, Florida; [3]University of South Florida College of Medicine, Tampa, Florida

*Objective:* We aimed to provide a classification of suicidality disorder phenotypes. The view that suicidality is transnosological and that all forms of suicide are the same is not consistent with existing evidence of patients' responses to pharmacological treatment. For example, antidepressants make suicidality better in some patients, worse in others, and are no better than a placebo for a third group. This suggests that there may be more than one type of suicidality.

*Design:* We employed a phenomenological approach in this study by observing in detail and directly communicating with subjects over time about their suicidality.

*Results:* We developed diagnostic criteria and a related structured diagnostic interview for 12 distinct suicidality disorder phenotypes, as follows: impulse attack suicidality disorders, homicidal suicidality disorders, psychotic suicidality disorders, obsessive-compulsive suicidality disorders, posttraumatic stress suicidality disorders, eating disorder/malabsorption suicidality disorders, substance-induced suicidality disorders, medical illness/neurological condition–induced suicidality disorders, anxiety disorder–induced suicidality disorders, mood disorder–induced suicidality disorders, life event–-induced suicidality disorders, and suicidality disorders that are not elsewhere classified. Among these phenotypes, the description for impulse attack suicidality disorders is new. This disorder is associated with unexpected, unprovoked, unpredictable attacks of an urgent need to kill oneself.

*Conclusion:* We offer 12 suicidality disorder phenotypes. Because these phenotypes may have a different response to treatment, each phenotype should be investigated separately when investigating antisuicidality treatments and when investigating the relationship between genetic and other biomarkers in suicidality.

*Funding/Disclosures:* Sheehan is the author, copyright and patent holder of scales (including S-STS), structured interviews, phenomena definitions, classifications, and books on suicidality; a nonlinear model and candidate drug treatments for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. He is a co-founder of Harm Research Institute and Harm Research Press and owns stock in and is a consultant for Nview Health, which distributes the computerized versions of his scales and structured interviews. Sheehan receives royalties from the licensing of his Suicidality measures. He is a consultant for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Seelos, Biogen, and Eisai and a presenter for Biohaven Pharma, Janssen Pharmaceuticals Inc., Sunovion, Allergan, Biogen, and Eisai. Giddens is the author and copyright holder of scales, phenomena definitions, classifications, and books on suicidality; a nonlinear model and a candidate drug treatment for suicidality; and a hypothesis for the mechanism of action of some antisuicidality medications. She is a cofounder of Harm Research Institute and Harm Research Press and is the editor of the *Science of Suicidality*. She is a consultant for Nview Health and Biogen.

## TRIAL METHODOLOGY

### Where did my early-termination central nervous system research subjects go and what other studies did they participate in?

*Authors:* Demonte M,[1] Amella D,[1] Li B,[1] Weingard KK,[1] and Efros MD[1]

*Affiliation:* [1]Verified Clinical Trials, Garden City, New York

*Objective:* We aimed to assess research subject behaviors and future clinical trial participation following early termination (ET) in central nervous system (CNS) clinical trials at United States (US) sites. Research subject retention in a particular study is a concern in clinical trials research. Research participants that voluntarily withdraw from a study that is ongoing affect the sample size and may jeopardize their own safety and the data integrity of the clinical trial. Poor-quality research volunteers will at times leave early from a study to join a new study or the same study again at a different location. There are many incentives and motives for this behavior. Verified Clinical Trials (VCT) is the largest global research subject database that tracks duplicate enrollment and research subject study status. VCT can follow ET frequency and also has the ability to determine what other studies the ET subjects then attempt to enroll in going forward.

*Design:* CNS ET data were collected from a global research subject database registry utilized at approximately 2,500 sites in the US from January 2017 through September 2019. Subject partial identifiers were entered into the database after completion of the site-associated institutional review board–approved consent form. ETs at research site locations were identified after entries were authenticated and compared with the subject's research history via a proprietary VCT algorithm. Subject behaviors in attempting inappropriate re-enrollment in the same study or in different studies, and travel distances were evaluated.

*Results:* Among the 2,213 ET subjects identified in 66 CNS trials, 33 caused 55 verification failure alerts; 12.7% of these were due to exclusionary research history (7/55), 34.5% to washout period truncations (19/55), and 11.0% to rescreening/re-enrollment attempts (6/55). Health condition cross-over

occurred in 34.32% of all subjects (23/67) and occurred in 21.2% of ET subjects causing verification failure alerts (7/33). The most common health condition for re-enrollment was depression. The average travel distance for all verifications for CNS studies was 99.69 miles and the median travel distance was 14 miles within 415 records. Average travel distance after initial study ET prevented by VCT was 91 miles and the median was 12 miles within 40 records. After filtering ETs, the mean travel distance of the rest of the verifications was 100.61 miles and the median was 14 miles within 375 records.

*Conclusion:* Tracking research subject study participation and enrollment status with a global research subject database is an important way to understand the scope of ET and prevent certain protocol violations in CNS trials. The frequency and outcome of ET research subjects' future study participation is a special consideration. While many research subjects will withdraw from a clinical trial for sound reasons, there exists a subset of research participants that do so for nefarious reasons. In some instances, this can be for monetary gain or for access to various potential free medical treatments and care. Of interest and concern is the number of subjects that voluntarily ET from a study only to join another clinical trial within their washout period. Without a research subject database registry, these 2,213 ET subjects would not have been identified and inclusion and exclusion protocol violation would not have been prevented. We argue that all sponsors should use such a registry at their CNS research sites to better understand subject behaviors, protect clinical trial subjects' safety, and improve data integrity.

*Funding/Disclosures:* All authors work for Verified Clinical Trials, whose research subject database registry was used in this analysis.

## Application of blinded predictive analytics in noncentral nervous system clinical trials

*Authors:* Everhart AT,[1] Daniel DG,[1] and Kott A[1]

*Affiliation:* [1]Signant Health, Wayne, Pennsylvania

*Objective:* Psychiatry clinical trials have relatively modest success rates (24% and 56%, respectively, in phases II and III) because they utilize relatively subjective endpoints and because drug–placebo differences are often modest. However, clinical trials in many medical fields, such as oncology, which utilize more objectively measured endpoints also have relatively low success rates (25% and 40%, respectively, in phases II and III). The relatively low success rate in oncology and many other medical clinical trials is multifactorial. Identification of markers of poor data quality would enable the rapid remediation of a poor measurement technique before it is replicated and potentially obscures any drug signal after randomization. Previously, we have reported data quality markers predictive of further measurement error, placebo response, and diminished drug–placebo differences in central nervous system (CNS) disorders. The same methodologies could lead to similar insights and benefits for non-CNS disease trials.

*Design:* Data from 4,245 subjects collected across 286 investigative sites participating in six atopic dermatitis clinical trials were monitored for anomalies in body surface area (BSA) assessments obtained during the administration of two rating scales: the Scoring Atopic Dermatitis (SCORAD) scheme and the Eczema Area and Severity Index (EASI). The analysis included the evaluation of discordance in BSA assessments between the two rating scales and the evaluation of erratic BSA results.

*Results:* The application of blinded data analytics identified investigative sites of concern based on discordant BSA results from the two atopic dermatitis scales and identified erratic results from individual raters at sites of concern.

*Discussion:* A straightforward approach to monitoring data quality is to assess for aberrant or illogical patterns of symptom change. This has been performed unobtrusively in the background in a risk-based model in CNS trials that includes remediation of aberrant raters and sites. Similarly, blinded data analytics can be employed in non-CNS disease trials to improve endpoint quality. Future applications of blinded data analytics should be considered in other dermatology diseases, immune-mediated diseases, and oncology, among others.

*Funding/Disclosures:* All authors are employees of Signant Health.

## Project RockSTARR: fostering connections to advocacy

*Presenters:* Arevalo C,[1] Carpenter-Conlin J,[1] Craig B,[2] Efros MD,[3] Weingard KK,[3] and Kramer L[4]

*Affiliations:* [1]Alkermes plc, Dublin, Ireland; [2]Pillar Clinical Research, Richardson, Texas; [3]Verified Clinical Trials, Garden City, New York; [4]The STARR Coalition, Little Rock, Arkansas

*Objective:* Project RockSTARR, a collaboration between Alkermes Inc., the STARR Coalition, and Verified Clinical Trials, is a pilot program that provides advocacy information to research participants in the ENLIGHTEN research sites and makes connections to advocacy organizations in their communities. ENLIGHTEN is the ongoing phase III clinical research development program investigating a novel treatment for schizophrenia and bipolar I disorder. The long-term objective of Project RockSTARR is to expand this program across multiple clinical trials and indications and to help reduce the stigma of mental illness and central nervous system clinical research.

*Design:* Patients at participating ENLIGHTEN research sites are provided informational handouts about preapproved, charitable advocacy organizations in their community. Patients are given the opportunity to direct a financial donation in a small, predetermined amount to a local advocacy organization of their choice. These financial donations are drawn from funds supplied by the sponsor and are separate from patient reimbursement for clinical trial participation. Donations made to patient-selected advocacy organizations are tracked in a blinded manner.

*Results:* The program creates a pathway for research participants to give back to their community with the following potential program benefits: participants learn about local advocacy organizations and gain access to information outside of the clinical research trial; advocacy organizations learn more about clinical research trials in their area and benefit from additional funding to support programming; research sites better understand the mission of advocacy organizations, their role in the community and in an evolving health care ecosystem: and connections are made between participants, advocacy organizations and clinical research.

*Conclusion:* Project RockSTARR appears

to be a viable and appropriate initiative for providing advocacy information to research participants in the ENLIGHTEN research sites and supporting their making of relevant connections with advocacy organizations.

*Funding/Disclosures:* Alkermes Inc. is providing the funding for this project.

**Broadening the empirical exploration of the placebo-control reminder script to reduce placebo and nocebo effects: a preliminary data analysis of subjects with schizophrenia and schizoaffective disorders**

*Authors:* Cohen EA,[1] Hassman H,[1] Walling DP,[2] Wyka K,[3] Grindell VM,[2] Glass SJ,[1] Ball RR,[1] Styczynski J,[1] Lobb JM,[1] Hazzard-Randolph D,[1] Joseph AV,[1] and Ereshefsky L[1,4]

*Affiliations:* [1]Hassman Research Institute, Science Division in Berlin, New Jersey; [2]Collaborative Neuroscience Network in Garden Grove, California; [3]Graduate School of Public Health and Health Policy, The City University of New York, in New York, New York; [4]The University of Texas in Austin, Texas

*Objective:* The placebo-control reminder script (PCRS) was first reported at the CNS Summit 2018 as being empirically validated to significantly manage the placebo effect among depressed subjects. The current investigation replicated that methodology to determine if the PCRS has a similar impact on subjects with schizophrenia/schizoaffective disorder.

*Design:* Schizophrenia/schizoaffective depressed adult patients from multiple sites were randomized to two groups. The intervention group (IG) subjects were read the PCRS before completing the Beck Depression Inventory-II (BDI-II). The script reviews key causes of the placebo effect, including participant expectations. Control group (CG) subjects were not read the PCRS. Depression but not psychosis was the dependent variable due to scale psychometrics and assessment duration. Adverse events were collected to assess the nocebo effect. Subjects were informed of the 50% chance of being assigned the placebo or the active drug, yet all received the placebo. Given this deception, subjects were provided a debriefing form at the end of the study revealing the investigation's true intent and procedures.

*Results:* IG and CG subjects did not differ in baseline characteristics, including BDI-II scores. IG subjects reported significantly ($p = 0.002$) higher BDI-II scores at the primary endpoint (IG: $M = 22.00$, $SD = 5.17$ vs. CG: $M = 17.17$, $SD = 5.63$). Four subjects (8.7%) reported adverse events; all were in the CG group ($p = 0.05$).

*Conclusion:* While more subjects need to be enrolled in the current investigation to confirm these findings, preliminary data suggests the PCRS continues to reduce the placebo and the nocebo effects among subjects with psychotic disorders. Future investigation recommendations will be discussed.

*Funding/Disclosures*: The authors report no funding sources or conflicts of interest exist.

**Recruiting patients with Rett syndrome by going directly to referral sources**

*Author:* Finlayson A[1]

*Affiliation:* [1]ClinEdge, Quincy, Massachusetts

*Objective:* ClinEdge was contracted to support participant recruitment for a rare disease clinical study involving patients with Rett syndrome, which is estimated to affect one in every 10,000 to 20,000 individuals, across five research sites. The sponsor was just over 12 months into study enrollment only having seven out of the 22 needed patient randomizations. Initially, recruitment was expected to be completed in 16 months. Unfortunately, this recruitment target was deemed a highly unlikely goal at the current run rate. The sponsor had already tried to contract with three other recruitment vendors that yielded minimal results and unfortunate high expenses. Therefore, when ClinEdge was contacted by the sponsor, there was visible frustration with low momentum. Since this disease involves behavioral symptoms, experience has shown that patients need to be classified rigorously and findings confirmed using objective measures to achieve robust results. With this theory, our mission was to address recruitment by providing a proactive solution that would be targeted at referral sources tailored to the patients' overall study experience and accommodations that would be provided.

*Design:* The clinical trial in question sought to enroll subjects aged four years or older with Rett syndrome (a rare, noninherited genetic postnatal neurological disorder that occurs almost exclusively in girls and leads to severe impairments affecting nearly every aspect of the child's life, including their ability to speak, walk, eat, and even breathe easily). As part of its initiative, ClinEdge executed a comprehensive outreach strategy that was titled internally as "Leave no Rett Syndrome Patient Behind." Our goal was to draw significant exposure by communicating and building relationships with all relevant clinical professionals and advocacy and support specialists. To do this, we implemented an adaptive communications structure that utilized both digital and grassroots channels while focusing on the uncommon clinical trials message of "As leaders at the forefront of care for the growing epidemic of Rett Syndrome, there is hope for your patients!"

For the digital campaign, we first reached out via social media and then using electronic newsletters from study-specific landing pages directly to medical organizations, physicians, key opinion leaders, bloggers, and advocacy and support groups, among others. For the grassroots campaign, we made cold calls and sent emails and texts to referring organizations in concert with a personalized outreach strategy that ensured each organization would have details on the study, indication, patient population, patient travel, and concierge experience.

Once an organization identified a patient, we connected them to the closest site and adhered to the following process: first, ClinEdge provided study-related materials to each referring physician, allowing the caregiver to make an informed decision about the study. Second, if the caregiver was interested in having their child participate, ClinEdge connected the caregiver with the closest site and provided the relevant contact information to the study staff.

Beyond physician referrals, ClinEdge established connections with support groups of the same general purpose; this route took on an added level of relationship-building for these families. Support groups provide a community for patients where they feel as though they belong and their voice is being heard. Outreach to these communities is important because, once a family has a positive experience, they are much more likely to share the study information with other families. ClinEdge was the liaison between the patients and study doctors, which gave us the opportunity to be a voice for the patient as well.

*Results:* Through a solid digital and grassroots outreach strategy, we cultivated more than 130 initial outreach targets, which included the following potential referral sources: neurologists, pediatric neurologists, neuropsychologists, pediatric pulmonologists, genetic counselors, developmental pediatricians, pediatricians (and adolescent medicine practitioners), nurse practitioners, social workers, psychologists/psychiatrists, speech–language pathologists, resource specialists, and Rett syndrome advocates. Within three short months, our outreach strategy had generated 10 solid patient referrals that were sent to five participating sites, with half of those randomizing and the others set to randomize over the next several months. ClinEdge's outreach strategy therefore allowed the sponsor to increase the rate of randomization for this rare indication and ultimately move towards faster study completion.

*Conclusion:* In an age when technology is projected to trump current clinical trial processes, the importance of providing the right services focused on relationship-building with a personalized touch still proactively can address important study recruitment barriers. Our goal was to open communication channels with the people that know the most about this disease other than the patients and caregivers themselves. It was essential that we were able to develop a highly customized recruitment plan for this type of indication and, no matter how "technological" or "automated" our industry becomes, such personalized strategies will always be required.

Trials in rare indications require innovative approaches designed to engage these patients in what can be challenging studies for the entire family involved. Through our experience, ClinEdge has developed an effective planning and execution process. In particular, ClinEdge has identified several critical success factors for rare disease studies, as follows:

- ClinEdge's evidence-based methodology provides access to proprietary databases, feasibility studies, and key investigator relationships to enhance patient recruitment.
- Strong partnerships with relevant patient advocacy groups can create stronger study awareness and support.
- Quality subject and patient support materials demonstrate the benefits of participation to subjects, leading to increased motivation to enroll.
- A core set of study-branded tools can help sites to identify potential patients as well as educate them about the study and its requirements.
- Targeted patient and caregiver outreach tactics involving comprehensive outreach and engagement tactics can facilitate improved enrollment rates.
- Comprehensive patient-centric solutions tailored to the country and region such as patient travel coordination, patient concierge, enrollment hotline, and artificial intelligence–based screening tools, among many others, are key.
- Offering our "Patients-first Site-activation Model" to fast-track our global site network after a patient has been identified can improve patient inclusion.

*Funding/Disclosures:* The author is an employee of ClinEdge.

**The perceptions of healthcare providers regarding clinical trials**

*Presenters:* Neubauer S,[1] Craig B,[1] Gutierrez N,[1] and Hudefi F[1]

*Affiliation:* [1]Pillar Clinical Research, Richardson, Texas

*Objective:* Recent literature continues to underscore the difficulties of recruiting clinical trial participants and the lack of direct referrals from health care providers. Various efforts have been made to understand participants' perceptions concerning clinical trials, but few studies have investigated health care providers' attitudes towards clinical trials. This qualitative phenomenological study examined 30 clinicians' perceptions of clinical trials.

*Design:* Semistructured online interviews were used to capture the essence of the participants' perceptions. The grounded theory approach was used for identifying themes related to the study's research questions. Grounded theory analysis consisted of (1) initial coding, (2) open coding, (3) axial coding, and (4) theoretical coding.

*Results:* A total of 30 participants from various health care disciplines including psychotherapists, primary care physicians, and nurse practitioners provided data that shaped the phenomenon. Themes that emerged consisted of a lack of awareness of local clinical trials, altruistic participation, concerns about adverse events, and trial enrollment as a last resort for treatment.

*Conclusion:* This study contributes to the understanding of health care providers' understandings and assumptions about clinical trials. These findings highlight the need for clinical trial professionals to disseminate reader-friendly information about the clinical trial process and the need for open dialogs between researchers and health care providers regarding clinical trial enrollment. The results also indicate a lack of understanding between health care professionals and clinical trial personnel. These insights have implications for health care and mental health care, indicating that more detailed information and education about clinical trial participation would be valuable.

*Funding/Disclosures:* The authors report no funding sources or conflicts of interest exist.

**The avatar will see you now: a new training tool for central nervous system clinical trials**

*Authors:* Busner J,[1] Silverman S,[1] Oakley M,[1] Kott A,[1] and Daniel DG[1]

*Affiliation:* Signant Health, Wayne, Pennsylvania

*Objective:* An avatar system was built as a novel tool for training interview skills, diagnostic assessment, and symptom measurement in central nervous system trials.

*Design:* In collaboration with an artificial intelligence group, a prototype avatar system was built that presented an avatar clinician interviewing an avatar depressed patient on a standard efficacy scale. The prototype allowed for configurable appearance and interview proficiency of the interviewer. Subjects were 10 clinicians (eight with a master's or doctoral level; one psychiatric nurse, one bachelor's level) who had been exposed to standard high-quality scale and interview skills training. Subjects viewed and scored the avatar patient as interviewed by a high-proficiency avatar interviewer. Subjects then viewed a low-proficiency avatar interviewer and identified interviewer errors made. Subjects were then shown 12 features of the prototype and asked to rate them on a five-point scale.

*Results:* Inter-rater scoring agreement was high (kappa = 0.95). Subjects identified 75% of embedded avatar interviewer errors. The mean value for the 12 features overall was 4.2.

The identified advantages included ease of use, as well as being hands-free, inclusive, and enjoyable. Identified concerns with the technology included problems understanding strong accents and privacy issues.

*Conclusion:* Subjects in our study achieved high interrater agreement when scoring the avatar interview and were able to detect the majority of errors made by the low-proficiency avatar interviewer. Subjects provided generally high likeability ratings, suggesting that this novel form of computer-generated rater training may engage and interest clinical trials rater in other training venues and with other efficacy and diagnostic scales. As many sponsors move to full or partial online rater training environments, an avatar training tool may help to enhance involvement and attention to trained messages provided.

*Funding/Disclosures:* The authors are all full-time employees of Signant Health. This abstract was presented in part at the American Society of Clinical Psychopharmacology Meeting in Scottsdale, Arizona on May 28–31, 2019.

**Decentralized trials in psychiatry: estimating the operational burden from completed hybrid trials**

*Authors:* Saxby BK,[1] McNamara C,[1] Director M,[1] and Di Clemente G[1]

*Affiliations:* [1]Cronos Clinical Consulting Services, Inc., Lambertville, New Jersey

*Objective:* The feasibility of "decentralized" or "site-less" clinical trials is being explored as a method of reaching otherwise inaccessible populations and increasing recruitment. Although removing regular clinic visits confers advantages to the participant, it presents a challenge to study conduct, particularly in psychiatry where outcome assessments rely on interactions with a rater. To provide insight into the operational burden, we examined a "hybrid" design wherein the primary outcome was a telephone-based assessment conducted by an independent rater.

*Design:* Metrics were aggregated over 30 months from five psychiatry studies and 21 countries, involving 1,962 patients and 142 raters. The cloud-based Cronos Integrated Research Platform (Cronos Clinical Consulting Services, Inc., Lambertville, NJ, USA) was used to schedule assessments and to send automated reminders to raters and participants. To quantify the operational burden, we examined the frequency and timing of rescheduled assessment calls and explored regional differences.

*Results:* Of 9,122 events that were rescheduled within 10 days, 3,211 (35.2%) took place within 12 hours and over 50% (1,856) of those were within four hours. These represented "forgotten" appointments or short notice unavailability for the call. As expected, rearranged calls diminished as time from the original appointment increased, while raters attempted to keep within the protocol window. There were no major regional differences between Western/Northern Europe, Eastern Europe, and North America, although South America had longer rescheduling durations.

*Conclusion:* While decentralized trials offer increased accessibility and flexibility for participants, the operational burden of study organization may be increased, and requires ongoing monitoring, particularly where participants are required to interact with study personnel in real time.

*Funding/Disclosures:* Saxby, McNamara, and Director are full-time employees and Di Clemente is the founder and president of Cronos Clinical Consulting Services, Inc., the developer and commercial provider of the Cronos Integrated Research Platform for use in clinical trials. ICNS